EFFECT OF INFECTED BILE IN POST OPERATIVE OUTCOME OF PANCREATICODUODENECTOMY

Dissertation Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the regulations

for the award of the degree of

M.CH (SURGICAL GASTROENTEROLOGY & PROCTOLOGY)
BRANCH –VI

INSTITUTE OF SURGICAL GASTROENTEROLOGY & LIVER TRANSPLANTATION

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA.

AUGUST 2009

CERTIFICATE

This is to certify that the dissertation entitled **" EFFECT OF INFECTED BILE IN POST OPERATIVE OUTCOME OF PANCREATICODUODENECTOMY"** is the bonafide original work of **Dr. S.M.SIVARAJ** in partial fulfillment of the requirements for **M.CH. (SURGICAL GASTROENTEROLOGY & PROCTOLOGY) BRANCH –** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in August 2009. The period of study was from June 2007 to April 2009.

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DECLARATION

I, **Dr. S.M.SIVARAJ,** solemnly declare that the dissertation titled, **"EFFECT OF INFECTED BILE IN POST OPERATIVE OUTCOME OF PANCREATICODUODENECTOMY"** is a bonafide work done by me at Govt. Stanley Medical College & Hospital during 2007-2009 under the guidance and supervision of **Prof.R.SURENDRAN, M.S., M.CH,** Professor and Head, Department of Surgical Gastroenterology, Stanley Medical College, Chennai-600 001.

The dissertation is submitted to Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.CH Degree (BRANCH – VI) in Surgical Gastroenterology & Proctology .**

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ACKNOWLEDGEMENT

I express my profound gratitude to **Dr. J. MOHANASUNDARAM, M.D., Ph.D, DNB,** Dean of Government Stanley Medical College and Hospital, Chennai–600001 for permitting me to use all the needed resources for this dissertation work.

I sincerely express my grateful thanks to **Prof R. SURENDRAN,M.S.,M.CH,** Professor and Head, Department of Surgical Gastroenterology, Stanley Medical College for his unstinted support and advice rendered throughout my study. I thank him for being a constant source of encouragement, inspiration, not only in this study but in all my professional endeavors.

I express my sincere thanks to all the Assistant Professors, **Dr P. Ravichandran, Dr.D.Kannan, Dr. T.G. Balachander, Dr S. Jeswanth, Dr. S. Rajendran, Dr. V.Vimalraj, Dr. E.Selvakumar, Dr. G. Rajarathinam and Dr. G.S. Prabhudoss** , Department of Surgical Gastroenterology, SMC, Chennai.

My sincere thanks to **Prof. Rosy Vennila** , Department of Microbiology for preparation of this study.

I also sincerely thank Ethical Committee, SMC, Chennai for approving my study.

I extend my sincere thanks to my subjects but for them the project would not have been possible.

I am greatly indebted to all my friends, Postgraduate colleagues who have been the greatest source of encouragement, support, enthusiasms, criticism, friendly concern and timely help.

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INTRODUCTION

Bactibilia:

Bile in normal subjects is sterile. This is brought about by various factors like the presence of biliary sphincter, antegrade flow of bile , mucus secretion of the biliary tract, antibacterial , anti fungal action of the bile salts , Ig A secretion , presence of hepatic tight junctions & other factors .(1)

Various pathologic conditions lead to bactibilia . Biliary obstruction is the most common condition associated with bactibilia .It results in increased pressure in the biliary system leading to breakdown of bile junction leading to cholangiovenous
reflux, obstruction leads to diminishing the physical barrier of flushing, decreased bile salt delivery in the intestine resulting in less bile salt mediated bacteriostatic / bacteriocidal activity, promoting bacterial overgrowth, subsequent t increased
translocation of bacteria into portal circulation .

In addition the jaundice associated with biliary obstruction causes decreased kupffer cell function. In the presence of the gall stones within the gallbladder or the biliary tree, positive cultures are seen in 15% to 50% and 70 to 90% respectively (2). Where as in complete ductal obstruction with malignancy 25% to 40% have positive cultures. If a preoperative bile stent had been placed 69% of bile cultures were

positive when a preoperative stent had been placed (3).

Source: Infection occurs from two main sources.

1. Bacteria invade the biliary tract locally ascending from the duodenum..Because the bacteriology of the duodeneum and the infected bile is similar , the ascending theory is plausible

2.Enteric bacteria translocate from intestine and are introduced into the liver & bile through the hepatic portal venous system .

Causative Organisms :

The type & the concentration of bacteria that are present in bile depend on the degree of obstruction , stasis, the presence of foreign bodies, whether the obstruction is from malignancy or benign causes . Common biliary pathogens include the enteric gram negative aerobes – E.coli, Klebsiella ad proteus Polymicrobial cultures are present in 67 % of infected bile cultures (4).

In patients with previous biliary instrumentation and in particular, patients who have had a history of previous long term antibiotic treatment , Psuedomonos, serratia, enterococcus and enterobacter species, may be present . Gram positive organisms, especially enterococcus faecalis that are present in bile are more common in patients who have undergone percutaneous instrumentation of the biliary tree.

Anaerobes are present only occasionally and typically in patients with poor functional reserve, complex biliary problems , long term biliary stenting . Bile cultures in patients with malignant causes

of biliary obstruction more commonly are klebsiella, enterobacter, streptococcus, enterococcus, and candida compared with patients with benign biliary obstruction. Enterococci faecalis bactibilia increased after antibiotic use with a 16% incidence before and 63% incidence after antibiotic use. When analyzing the correlation between preoperative bile bacteria and post operative complications only enterococcus species were associated with the occurrence of complications (5)

Bactibilia & Post operative outcomes in Hepato biliary & Pancreatic surgery

Bactibilia is associated with increased post operative infectious complications(6,7) Other risk factors include foreign bodies(stents, drains), functional reserve of the patient, preoperative sepsis, blood transfusion & shock(8)

Prevention & treatment

In patients undergoing Hepato biliary & pancreatic surgery preoperative obstruction, bactibilia , & jaundice with their physical,chemical, immunologic consequences put the patient in significant risk for infectious complications. Prophylatic antibiotics that cover enteric gram negative aerobes, anaerobes and skin flora should be given . If the patient has an indwelling biliary catheter , if possible , cultures of bile should be taken before any surgery and antibiotics should be tailored to the particular bacteria present in the bile and their corresponding antibiotic sensitivity . Oral bile salts may be employed to replenish the bile salt stores in patients with obstructive jaundice .

The role of biliary stenting is controversial. External stenting to relieve biliary obstruction has been shown consistently to increase the complication rate in patients undergoing pancreato biliary

surgery and is thought to be secondary to the introduction of bacteria directly into the biliary tree. External stenting is reserved for cases of cholangitis that cannot be relieved by internal stenting and non surgical palliation of high biliary obstruction . Internal stenting to relieve biliary obstruction preoperatively in patients undergoing pancreatobiliary surgery is more controversial . Theoretically internal stenting avoids the introduction of exogenous bacteria and it corrects the detrimental effects of biliary obstruction and reduced bile salt delivery into the gut. clinical trials have yet to establish firmly the role of internal stenting in this setting.

Pancreatico duodenectomy , Bactibilia & Postoperative Outcome

Bile contamination has been reported as a major risk factor of postoperative sepsis after cholecystectomy (9) & hepatectomy (10) However with Preoperative antibiotic therapy was given for high risk acute cholecystitis patients compared with low risk cholecystitispatients there was no significant difference in post operative infectious complications following Cholecystectomy (11)

Povoski etal (12) reported a higher rate of infectious complications in patients with preoperative biliary drainage . They explained their results by negative effect of infected bile .In prospective randomized controlled trial by Lai et al(13) there was no

difference in infectious complications between stented and non stented groups.

In another trial by Lygidikas etal (14) authors found increased incidence of biliary infection in non stented group. In of view this contradicting results Belghiti et al(15) conducted a retrospective analysis & reported that bile infection is related to

previous biliary endoscopy in 80% of patients and is associated with an increased rate of post operative infections and advocated a specific antibioprophylaxis should be evaluated .

Consequently one possible way to reduce the morbidity after pancreaticoduodenectomy is to decrease the incidence of infectious complications associated with infected bile .

The concept of preoperative biliary drainage

The concept of PBD has been developed to reduce the postoperative morbidity and mortality in patients with obstructive jaundice, caused by a suspected pancreatic/periampullary malignancy. However, PBD, both endoscopic or percutaneous, is associated with an increased incidence of postoperative morbidity [mostly infectious complications] and postoperative mortality when performed prior to a pancreatoduodenectomy. Furthermore, the techniques used for PBD harbour their own complications. Therefore, the overall conclusion not to routinely perform preoperative biliary drainage seems evident. Nevertheless, still the majority of these patients undergo preoperative drainage, often preceded by a diagnostic endoscopic retrograde cholangiopancreatography (ERCP). Unfortunately, most of the available literature addressing the efficacy of PBD suffers from methodological flaws (e.g. differences in drainage procedures, duration of drainage, internal vs. external drainage, surgical procedures, small sample size) or is outdated

AIM OF THE STUDY

The aim of present study was to determine association between bile infection and invasive preoperative investigations and its influence on morbidity and mortality following pancreatico duodenectomy.

REVIEW OF LITERATURE

Pancreaticoduodenectomy (PD) is currently performed in high-volume centers, with a very low mortality. Reduced mortality rates result from careful patient selection, improved intraoperative management, and better postoperative care. Unfortunately, the decrease in operative mortality after PD has not been associated with a similar reduction in morbidity rates, which still range from 40% to 75%(16,17,18,19) and septic complications are responsible for approximately one third of postoperative morbidity (20,21)

Evidence for role of infected bile in septic & post operative complications following pancreaticoduodenectomy

1.Evidence in favour of increased septic & post operative complications

Role of Infected bile in association with post operative outcome is controversial . Its role in increasing wound infections is universally reported by many studies. But association with other septic complications like intra abdominal abscess , bacteremia & other complications of pancreaticoduodenectomy is controversial. Povoski (12)et al retrospectively analyzed 161 consecutive patients undergoing pancreaticoduodenectomy in whom intraoperative bile cultures were performed.

Microorganisms were isolated from 58% of these intraoperative bile cultures, with 70% of them being polymicrobial. Postoperative morbidity was 47% and mortality was 5%. Postoperative infectious complications occurred in 29%, most commonly wound infection (14%) and intra-abdominal abscess (12%). Eighty-nine percent of patients with intra - abdominal abscess (P = 0.003) and 87% with wound infection (P = 0.003) had positive intraoperative bile cultures. Microorganisms in the bile were predictive of microorganisms in intra abdominal abscess (100%) and wound infection (69%).

Multivariate analysis of preoperative and intraoperative variables demonstrated that preoperative biliary drainage was associated with positive intraoperative bile cultures (P <0.001), postoperative infectious complications (P = 0.022), intra-abdominal abscess (P = 0.061), wound infection (P = 0.045), and death (P = 0. 021). Preoperative biliary drainage increases the risk of positive intraoperative bile cultures, postoperative infectious morbidity, and death. Positive intraoperative bile cultures are associated with postoperative infectious complications and have similar microorganism profiles.

Belghiti (15)et al in a study, demonstrated bile contamination had a notable influence on immediate outcomes after PD for tumor, with a higher rate of infectious complications, particularly wound and intraabdominal abscesses.They also demonstrated a marked correlation between positive bile culture, length of stay in intensive care unit and rate of prolonged postoperative antibiotherapy. Bile contamination was present mainly in patients with ampulloma and those who had preoperative endoscopic procedures, including patients classified ASA 2 because of comorbidity. In addition, bile microorganisms were frequently resistant to antibiotics. They also observed that microorganisms in bile were predictive of microorganisms in many infectious complications. Indeed, germs isolated from abdominal abscesses were identical to those present in bile in 50% of patients, which is slightly lower than the 65% to 100% rates previously reported.[6, 16, 22] More interestingly, germs responsible for septicemia and infection of central venous access were identical to bile germs in 33% of patients. The microbial etiology of these postoperative infections strongly suggests that some of them resulted from contamination by biliary organisms during operation.

1.Evidence against increase in septic & post operative complications

In contrast Pundzius(22) et al,reported that bile infection did not increase statistically significantly the number of postoperative septic complication They evaluated etiology and the impact of bile infection on development of post-operative

complications. Patients were divided into groups according to results of intraoperative bile culture. Data on 64 patients, undergoing pancreatoduodenectomy at Kaunas University of Medicine Hospital between 2002 and 2004 were collected prospectively. In 31 patients (48.4%) intraoperative bile cultures were negative,

while in remaining 33 patients (51.6%) infected bile was documented. Both patient groups were homogenous according to demographic data, preoperative and intraoperative variables. Pancreaticoduodenectomy was performed in 21 patients after

preoperative biliary drainage (endoscopic stenting, bilidigestive anastomosis or percutaneous bile drainage), others (n=43) had primary operation. Infected bile was found more often in patients who underwent biliary drainage ($p<0.0001$). Among 43 patients with primary pancreaticoduodenectomy 22 patients underwent endoscopic retrograde cholangiopancreatography without stenting, while remaining 21 had no

preoperative endoscopic manipulation. Infected bile was present in 9 patients after endoscopic retrograde cholangiopancreatography (40.9%) and in 4 without preoperative endoscopy (19%). Enterococcus and Escherichia coli dominated in

bile cultures of patients with primary pancreaticoduodenectomy, while multiple species (3 and more microorganisms) dominated following drainage procedures. Septic postoperative complications were identified in 26.6% of cases. Infected bile did not influence both overall and septic postoperative complications. Bacteria

causing abdominal cavity and wound infections matched bile cultures in 7.7% of cases only. Pundzius

conluded that infected bile is found more often after preoperative biliary drainage procedures. However, bile infection did not increase statistically significantly the number of postoperative septic complication.

Gouma(23) etal reported that bacterial contamination of bile was significantly more common when an endoprosthesis was used, but did not result in a higher rate of infective complications. 57% patients had postoperative complications. There was no significant difference in the incidence of postoperative complications between

patients who had preoperative biliary drainage and those who did not ($p = 0.4$).

Evidence for influence of preoperative biliary drainage on development of post operative complications

To date, the influence of preoperative biliary drainage on development of postoperative septic complications is not unequivocally defined. Several clinical

trails revealed significantly increased rate of septic complication after pancreatoduodenectomy following biliary drainage . Others have reported that preoperative biliary drainage and bile infection were not associated with increased

rate of postoperative morbidity and mortality rates I

n contrast, Marcus et al. have shown that preoperative biliary drainage decreased the number of overall and infectious postoperative complications (24).

Large Retrospective analyses reporting significantly increased rate of septic complication after pancreatoduodenectomy following biliary drainage

1. In a retrospective study by Aranha(25) et al authors found no differences with respect to operative mortality (2%), incidence of pancreatic fistula (10% versus 14%), or intraabdominal abscess (7% versus 5%). Wound infection occurred more often in the stented group (8% versus 0%, $P = 0.039$).

In retrospective study by lillemoe(26) et al the overall complication rates were 35% in those who had stents placed and 30% in those

who did not (P = NS), patients with stents experienced a significantly increased incidence of pancreatic fistula (10% vs. 4%; P = 0.02) and wound infection (10% vs. 4%; P = 0.02). The incidences of other postoperative complications were similar between the stented and unstented groups.

2. V K Kapoor(27) et al analysed 121 PDs performed for periampullary tumors between 1989 and 1998. 54 patients were operated following a PBD while 67 patients were operated without PBD. 50 patients underwent internal biliary drainage while 4 patients underwent external biliary drainage. Stented patients had a higher incidence of wound infection (43 vs. 24%; p = 0.03), intra- abdominal abscess (28 vs. 15%; p = 0.06), pancreaticojejunal anastomotic leak (20 vs. 5%; p = 0.01) and overall infective complications (52 vs. 29%; p = 0.01), and a higher overall infective complication (52 vs. 27%; p = 0.02). The mortality rates were not significantly different The authors concluded that patients with PBD have more infective complications.
3. Makoweic(28) et al evaluated results after PHR with bilioenteric anastomosis and included data on intraoperative bile colonization . From 1994 to 3/2006 455

patients underwent PHR with bilioenteric anastomosis (74% PPPD, 16% Whipple, 8% duodenum-preserving PHR, 2% pancreatectomy). Indications for PHR were pancreatic or periampullary cancer (52%), chronic pancreatitis (38%) or others (10%). The results of intraoperative bile cultures (IBC) were available in 76% of the patients. Forty-eight percent had undergone PBD (44% endoscopically (endoPBD), 4% as PTCD). Data were gained by retrospective analysis of prospective pancreatic database. Operative mortality was 2.6 %. Surgical complications occurred in 32.5%, infectious complications (intraabdominal and/or wound infection) in 17.8%. Pancreatic

leakage was documented after 13.8% of the PHR. Endoscopic preoperative biliary drainageVs no PBD was associated with a reduced Surgical Complication rate (28% vs. 36%, p=0.06) but showed no significant reduction in individual complication types. Patients with PTCD (n=20; vs no PTCD) had a slightly higher Surgical Complication rate (45% vs 32%, p=0.16) especially because of significantly more Infectious Complication (35% vs 17%, p=0.04). Pancreatic leakage and mortality were not influenced by presence or type of PBD. In the subgroup of 344 cases with available Intra operative Biliary Culture. 174 (51%) had undergone PBD. Here, 216 patients (63%) had positive Culture. Positive Culture occurred in 91% after previous PBD but only in 9% in patients without PBD. A positive culture (vs.

negative) did not influence total Surgical Complication rate (31% vs. 35%) but was associated with significant more abdominal abcesses (12% vs 4%, $p<0.05$).The author concluded that Percutaneous PBD increases infectious complication rates after PHR. Endoscopic PBD is not associated with a higher overall complication rate salthough it promotes bile colonization which may lead to more abdominal abscesses.

Large Retrospective studies supporting preoperative biliary drainage and bile infection were not associated with increased complications

1. In a retrospective study by Gouma(23) et al bacterial contamination of bile was significantly more common when an endoprosthesis was used, but did not result in a higher rate of infective complications. 163 Whipple's resections were performed. 137/241 (57%) patients had postoperative complications. There was no significant difference in the incidence of postoperative complications between patients who had preoperative biliary drainage and those who did not ($p = 0.4$).

2. In a Consecutive series of 241 patients by Karsten (29)et al 184 patients underwent preoperative biliary drainage. Endoscopic drainage was the most

effective, shown by a median reduction in bilirubin concentrations of 82%, 74%, and 50% after endoscopic drainage ($n = 149$), papillotomy ($n = 25$) and external drainage ($n = 10$), respectively. Bacterial contamination of bile was significantly more common when an endoprosthesis was used, but did not result in a higher rate of infective complications. 137/241 (57%) patients

had postoperative complications. There was no significant difference in the I ncidence of postoperative complications between patients who had preoperative biliary drainage and those who did not ($p = 0.4$).

3. Buchler et(30) al in a retrospective analysis performed in a consecutive series of 257 patients undergoing pancreatoduodenectomy between November 1993 and November 1999 analysed ninety-nine patients (38%) who underwent preoperative biliary drainage for a median time period of 10 days (range 1 to 41) prior to resection. Cumulative postoperative morbidity was 47% (120 patients), the reoperation rate was 4.3% (11 patients), and mortality was 2.3% (6 patients).

There was no difference in total morbidity, infectious complications, reoperation rate, mortality, or long-term survival between patients with or without preoperative biliary drainage.

4. Marcus(24) et al from Newyork school of medicine evaluated the influence of preoperative endoscopic biliary drainage (EBD) on morbidity after PD for malignant biliary obstruction by retrospective study. Length of postoperative hospitalization for patients undergoing Endoscopic Biliary Drainage was 13.5 days, compared with 19 days for patients who were not drained ($p = 0.02$). Patients who were not drained tended to have more overall complications ($p = 0.054$). Multivariate analysis revealed time to regular diet ($p < 0.0001$) and no preoperative drainage ($p = 0.04$) to be independent factors significantly increasing the length of hospitalization. Endoscopic biliary drainage before PD significantly reduced the length of postoperative hospitalization and was associated with less postoperative morbidity. Further studies, including cost analysis, are warranted.

Prospective Randomized Controlled trials on Pre operative biliary drainage &post operative outcome

1. In a RCT by Hatfield(31) in 1982 et al 57 patients with obstructive jaundice were randomly allocated to surgery with preoperative external biliary drainage (29 patients) and without preoperative external biliary drainage (28 patients). 22 patients ultimately underwent laparotomy after a mean of 11.7 days of drainage and 25 had surgery without preoperative drainage. The postoperative complication rate was low and similar in both groups but complications associated with the drainage procedure were substantial. Perioperative mortality was 4/28 (14%) in the drainage group and 4/27 (15%) in the non-drainage group. There seems to be no advantage associated with routine preoperative external biliary drainage before surgery for obstructive jaundice

2. Mc Pherson (32) in 1982 started a controlled clinical trial of pre-operative percutaneous drainage was started at the Royal Postgraduate Medical School. At the time of percutaneous transhepatic cholangiography patients were randomized either to laparotomy or to pre-operative percutaneous transhepatic biliary drainage (PTBD) followed by laparotomy. Only patients with malignant biliary tract

bstruction and serum bilirubin greater than 100 mumol/l were included. Seventy patients entered the trial, and five were withdrawn. Of the 65 remaining, 31 underwent laparotomy and 34 had pre-operative PTBD followed by laparotomy. The median duration of drainage was 18 days and during this time the median bilirubin fell from 305 to 115 mumol/l. Five patients required early surgery for complications of PTBD and two died within 30 days of surgery. The mortality for laparotomy was 19 per cent (6/31) compared with 32 per cent (11/34) for drainage plus laparotomy. This trial highlights the hazards of PTBD in high risk patients and has failed to demonstrate a reduction in mortality with the use of pre-operative PTBD .

3. A prospective, randomized study was performed by H A Pitt(33)et al (1985) to determine the effect of preoperative PTD on operative mortality, morbidity, hospital stay, and hospital cost. Thirty-day mortality was 8.1% among 37 patients undergoing preoperative PTD, compared to 5.3% for 38 patients who went to surgery without preoperative drainage. Overall morbidity was also slightly, but not significantly, higher in patients who underwent preoperative PTD, (57% versus 53%). However, total hospital stay was significantly longer (p less than

0.005) in the PTD group (31.4 days versus 23.1 days). The cost of this excess hospitalization and the PTD procedure at our university medical center was over +8000 per patient. The authors conclude that preoperative PTD does not reduce operative risk but does increase hospital cost and, therefore, should not be performed routinely.

4. In a prospectively randomized controlled trial by Lai(34) et al there was no difference in post operative outcome between stented and non stented groups

Systematic reviews on Pre operative Biliary drainage

1. In a systematic review by Johnson etal(35) in 2001 Using Medline a literature search was performed for papers published in English from January 1980 to October 2000, using the text words 'obstructive jaundice', 'preoperative', 'drainage' and 'stent'. All retrieved papers which reported experimental or clinical observations relevant to the study aim were carefully analysed and the findings are summarised in this review. There is no evidence in the literature to support the view that routine PBD improves postoperative morbidity and mortality in patients

with obstructive jaundice undergoing resection. PBD has its own complications that cancel out its benefits. However, PBD could be beneficial in patients presenting with sepsis, coagulation abnormalities or malnutrition.

2. Wang et al (36)searched The Cochrane Hepato-Biliary Group Controlled Trials Register (CHBG), the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, the Chinese BioMedical Literature on disc (CBM disc), and the Chinese Medical Current Contents (CMCC). All databases were searched up to October 2006.Author considered for inclusion randomised clinical trials comparing biliary drainage followed by surgery and direct surgery performed for obstructive jaundice.They collected the available data on the characteristics of the trial, methodological quality of the trials, mortality, morbidity, and hospital stay as reported in each trial. Data were analysed with both the fixed-effect and the random-effects models, using RevMan Analysis. For each outcome, odds ratio was calculated with 95% confidence intervals (CI) based on intention-to-treat analysis.Five trials with 320 patients (160 in each group) were included. Four trials (n = 235) compared percutaneous transhepatic biliary drainage with direct surgery, and one

trial (n = 85) compared pre-operative endoscopic drainage with direct surgery. All trials were of low methodological quality. There was no significant difference in mortality (OR 1.14, 95% CI 0.60 to 2.10) between the pre-operative biliary drainage group and the direct surgery group. No significant difference was found in mortality (OR 1.16, 95% CI 0.56 to 2.41), overall morbidity (OR 1.35, 95%CI 0.48 to 3.83), and in different complications between the percutaneous transhepatic biliary drainage group and the direct surgery group. The trial comparing pre-operative endoscopic drainage and direct surgery showed no significant difference in mortality (OR 1.09, 95% CI 0.32 to 3.68), but found higher morbidity in the endoscopic drainage group. The overall

hospital stay was 8 to 17 days shorter in the direct surgery group.Our analyses neither supports nor refutes pre-operative biliary drainage for patients with obstructive jaundice needing surgery. In some specific lesion site it may cause more complications. Pre-operative biliary drainage also prolonged hospital stay and increased cost.However, the strength of evidence is low because of the poor quality of the included trials. The authors concluded that more rigorously designed randomised clinical trials with larger sample size and advanced techniques and drugs are needed.

Meta Analysis on preoperative biliary drainage & post operative complications

1. Saleh et al(37) in their primary analysis, 337 patients underwent preoperative endoscopic biliary stent placement, and 412 patients had no endoscopic biliary stent placement (controls). The overall odds ratio for postoperative complications (stent vs. no stent) is estimated as 0.79: 95% CI [0.36, 1.73] and the estimated odds ratio for postoperative mortality is 0.81: 95% CI [0.33, 1.99]. In the secondary analysis, 1008 patients underwent preoperative EBS

   versus 720 control patients. The odds ratio for postoperative complications in this analysis was 0.93: 95% CI [0.65, 1.33] and for postoperative mortality is 1.12: 95% CI [0.62, 2.01]. authors concluded that no evidence was found of either a positive or adverse effect of preoperative endoscopic biliary stent placement on the outcome of surgery in patients with pancreatic cancer

2. Sewnath et al(38) analysed five randomized controlled studies comprising 302 patients met the inclusion criteria for level 1 studies, and 18 cohort studies comprising 2,853 patients met the criteria for level 2 studies. Meta-analysis of level 1 studies showed no difference in the overall death rate between patients who had PBD and those who had surgery without PBD. The overall complication

ate, however, was significantly adversely affected by PBD compared with surgery without PBD. At level 2, there was no difference in the death rate between the two treatment modalities. The overall complication rate, however, was significantly adversely affected by PBD compared with surgery without PBD. If PBD had been without complications, then

complications would be in favor of drainage based on level 1 studies, and no difference based on level 2 studies. Further, PBD was not able to reduce the length of postoperative hospital stay compared with surgery without PBD; instead, it prolonged the stay. The author concluded that PBD with current standards for patients with obstructive jaundice resulting from tumors carries

nobenefit and should not be performed routinely. The potential benefit of PBD in terms of postoperative rates of death and complications does not outweigh the disadvantage of the drainage procedure. Only if PBD-related omplications could be reduced by 27% and consequently diminish hospital stay could PBD be beneficial. Further randomized controlled trials with improved

PBD techniques are necessary.

Evidence that duration of stenting influences the Biliary infection & outcome of pancreaticoduodenectomy

Jagannath(39) et al analysed 144 patients undergoing pancreaticoduodenectomy from 1992 to 2001. Variables included biliary stenting, duration of stenting, stent complications and bile culture results. Patients were grouped as stented and non-stented. Factors likely to affect postoperative mortality and morbidity were

analysed. Preoperative biliary stenting was performed in 74 of the 144 patients. After surgery there were nine deaths (6.3 per cent) and 60 (41.7 per cent) of the 144 patients developed complications, with no significant difference in morbidity rate between stented and non-stented patients. Logistic regression showed that a positive intraoperative bile culture was the only factor significantly associated with operative morbidity ($P < 0.001$) and mortality ($P = 0.019$). Biliary stenting was not significantly associated with a positive culture ($P = 0.073$), but stenting that resulted in complications ($P = 0.006$)

and drainage for less than 6 weeks (P = 0.011) was associated with significantly greater culture positivity. Stenting followed by complications was shown by logistic regression to be the only factor significantly associated with a positive culture (P = 0.012). The authors concluded that positive intraoperative bile culture was associated with higher morbidity and mortality rates following pancreaticoduodenectomy. A positive culture in the stented group was related to stent complications and duration of stenting. Uncomplicated stenting was not associated with increased morbidity or mortality.

Evidence of specific antibioprophylaxis for contaminated bile with high risk of post operative infective complications

In patients with contaminated bile, antibioprophylaxis should be adapted to susceptibility results and, if needed, prolonged for an additional 48hours. The value of a 48- hour treatment is supported by the study of Karsten and coauthors,[22] who reported, in patients operated on between 1983 and 1992, a similar rate of infectious complications in patients with contaminated and sterile bile after a 48-hour therapy of amoxicillin-gentamicin combination. Because the possible emergence of nosocomial germs resistant to antibiotics, this approach should be used only in patients carrying a high-risk for bile contamination and must be followed by close evaluation of infectious complications

MATERIALS & METHODS

PATIENT SELECTION

Between May 2007 and April 2009, 51 consecutive patients underwent Pancreaticoduodenectomy with routine bile culture at our institution. This study compared two groups: one with positive bile culture (group A n = 23), and the other with sterile bile (group B, n =28)

SURGICAL PROCEDURE

After induction of anesthesia, all patients received intravenous antibioprophylaxis with cefazolin (2 g, followed by 1 g every 4hours). At the beginning of the procedure, patients had bile sampling from the common bile duct for bacterial examination and study of susceptibility to antibiotics. ancreaticoduodenectomy without pylorus preservation was performed with lymphadenectomy including nodes of the peripancreatic groups, hepatic pedicle, and right aspects of both celiac axis and superior mesenteric artery. Reconstruction was routinely performed with pancreaticogastrostomy, hepaticojejunostomy, and gastrojejunostomy. Octreotide 100 μg subcutaneously 3 times

per day was given only to patients with a soft pancreas and was started at the time of operation. The abdominal cavity was drained routinely using an open silicone drain. Oral diet was initiated 7 days after operation in patients without pancreatic leak or other intraabdominal complication.

PREOPERATIVE, PERIOPERATIVE, AND POSTOPERATIVE CLINICAL DATA

Preoperative, perioperative, and postoperative clinical data were collected**.** Preoperative comorbidities (including diabetes mellitus, hypertension, and coronary artery disease) were recorded. Preoperative endoscopic procedures included endoprosthesis insertion, isolated sphincterotomy, and ERCP without sphincterotomy. These endoscopic procedures had been performed in 8 of 10 patients before referral to our Institution . 2 patients underwent ERCP sphincterotomy & stenting in our institution. In both groups, no patients received neoadjuvant therapy. Intraoperative data included duration of operation, blood loss, and transfusion. Postoperative morbidity included postoperative death, pancreatic fistula, delayed gastric emptying, hemorrhage, renal insufficiency, and infectious complications. The number of patients treated by postoperative antibiotherapy for more than 7 days was recorded. Postoperative lengths of hospital stay were also noted.

INFECTIOUS COMPLICATIONS

All infections were proved bacteriologically by positive culture. Wound infection was defined as presence of pus requiring wound opening. Intraabdominal abscess was defined as postoperative fluid collection treated by puncture or drainage. Respiratory infection was defined as a suggestive radiographic study with fever and requirement for antibiotics. Septicemia was defined as positive

peripheral blood culture. Types of microorganisms isolated from intraabdominal collections, blood, and bronchial aspirates were compared with those from operative bile samples.

OTHER COMPLICATIONS

Delayed gastric emptying was defined as the need for nasogastric decompression beyond the 10th postoperative day. Pancreatic fistula was defined by one of the following criteria: amylase level in surgical drainage fluid more than three times the serum amylase after postoperative day 3**,** or by an amylase-rich (more than three times the serum amylase level) fluid collection, whatever its location. All patients with pancreatic fistula

ere treated with total parenteral nutrition, nasogastric aspiration, and somatostatin analogues. A major postoperative complication was defined as death, need for reoperation, intraabdominal hemorrhage (distinct from gastrointestinal bleeding), fistula of any origin, pulmonary infection, intraabdominal abscess, septicemia, or renal insufficiency.

STATISTICAL ANALYSIS

Values were expressed as means ± standard deviations, or median and range as appropriate. Statistical analysis of qualitative variables was performed using the chi-square test, and quantitative variables were tested using the student t-test test. A difference was considered statistically significant when $p< 0.05$.

RESULTS

Table 1 . Clinicopathologic and Biochemical Characteristics of Patients

Patient characteristics	Positive bile culture (n=23)	Negative bile culture (n =28)	p Value
Gender (male/female)	15/8	19/9	0.84 NS
Median age, y (range)	50.3	50.5	0.97 NS
Comorbidity			
Diabetes mellitus	8	10	1 NS
Hypertension	6	7	0.92 NS
Coronary artery disease	3	2	0.64 NS
Preoperative blood tests*			
Serum bilirubin (mg/dL)	9.5	11.0	0.56 NS
Hemoglobin, (g/dL)	10.5	11.2	0.776 NS
Serum creatinine (mg/L)	0.96	0.78	0.15 NS
Albumin(g/dl)	3.43	3.76	0.074 NS
Pathology			
Pancreatic ductal adenocarcinoma	2	6	0.11 NS
Periampullary carcinoma	19	19	0.22 NS
Distal bile duct carcinoma	2	2	0.61 NS
Duodenal carcinoma	0	1	0.45 NS
Cholangitis	2	0	0.19 NS
Pancreatic remnant (soft/hard)	8	10	1 NS
MPD size			0.818 NS

Table 1 . Clinicopathologic and Biochemical Characteristics of Patients

Patient characteristics	Positive bile culture (n=23)	Negative bile culture (n =28)	p Value
>3mm	16	19	
<3mm	7	9	
Preoperative endoscopic procedures			
Overall	8	2	0.02
ERCP	8	2	
Sphincterotomy	8	2	
Endoprosthesis	8	2	

Demographic, Clinical, Biochemical, Pathological characteristics are listed in table 1.

Both the groups were comparable in demographic ,comorbidity, biochemical parameters, & pathological characteristics.

There was no increase in biliary infection in patients with comorbidities like diabetes(p=1), hypertension (p=0.92), coronary artery disease(p=0.64)

There was no difference in biliary infection with the pathology of the obstruction.

Two patients in infected bile group had preoperative cholangitis as evidenced by jaundice , fever , right hypochondrial tenderness . (p=2).This difference is stastitically significant.

The other variables like hypothesised to increase the morbidity in some studies like soft remnant pancreas(p =1) & Main pancreatic duct diameter <3mm(p=0.818) was also equally distributed among both groups .

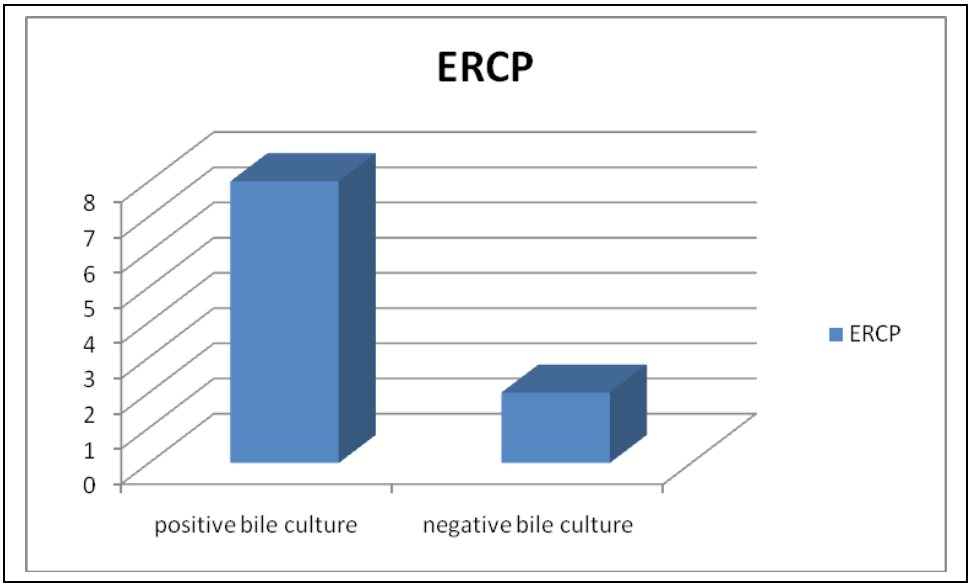
ERCP , sphincterotomy ,& stenting was significantly associated with positive bile culture(p

<0.02).The Odds ratio was 6.93. The 0.95 confidence interval was between 1.29 to 37.00

ERCP

		0.95 C.I. Low	0.96 C.I high
Risk ratio	2.18	1.31	3.63
Odds ratio	6.93	1.29	37.00

Of 10 patient who had undergone ERCP 8 patient (80%) had positive bile culture.



INTRAOPERATIVE RESULTS

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Table 2 . Intraoperative Parameters

Intraoperative parameters	Positive bile culture (n = 23)	Negative bile culture (n = 28)	P Value
Operative time (min) (Mean)	332(300–360)	326.(240–360)	NS
Blood loss (mL) (Mean)	300(200–900)	314s(100–900)	NS
Transfusions (U red cells) (Median)	0 (0–4)	0 (0–4)	NS

Intraoperatively , the mean operative time was 324 for positive bile culture group & 312 for negative bile culture group .

Mean blood loss was 382 ml in the cases & 340ml in the control group

Mean transfusions was nil in both groups , ranging from nil transfusion to 4 units in both groups

None of these values were statistically significant.

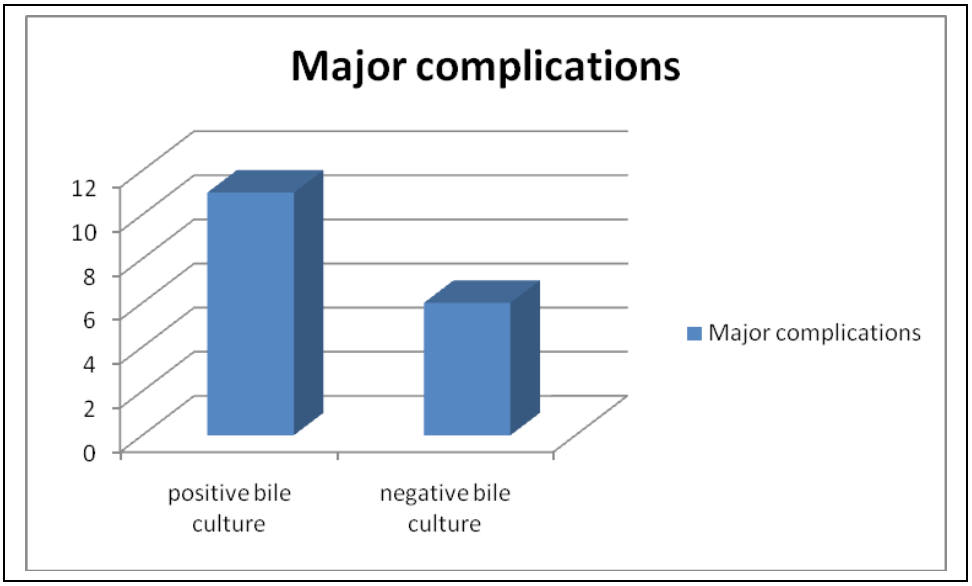
POSTOPERATIVE RESULTS

One patient in the negative bile culture a known case of poly cystic kidney disease and chronic renal failure with periampullary carcinoma died of ARDS.

Table 3 . Postoperative Complications and Lengths of Stay

Postoperative results	Overall (n =51)	Positive bile culture (n = 23)	Negative bile culture (n = 28)	p Value
Death, n	1	0	1	NS
Patients with one or more Major complications, n	17	11	6	0.0465
Infectious complications, n	18	12	6	0.022
Pancreatic fistula, n	4	2	2	1 NS
Delayed gastric emptying, n	6	4	2	0.3 NS
Renal insufficiency, n	6	5	1	0.05
Hemorrhage, n				
Intra luminal	1	0	1	1 NS
Intra peritoneal	1	1	0	0.45NS
Septicemia,n	7	6	1	0.03
Hospital stay , days	15.7	19.8	12.3	0.0001

Major Complications – POPF,DGE, Septicemia, Renal insufficiency , Pulmonary,or Haemorrhage,



Major complications developed in 11 patients in positive bile culture group and 6 in negative culture groupwith a significant P value of 0.0465. Theodds ratio 3.208 with a 0.95 Confidence interval from 0.9456 to 10.8858.

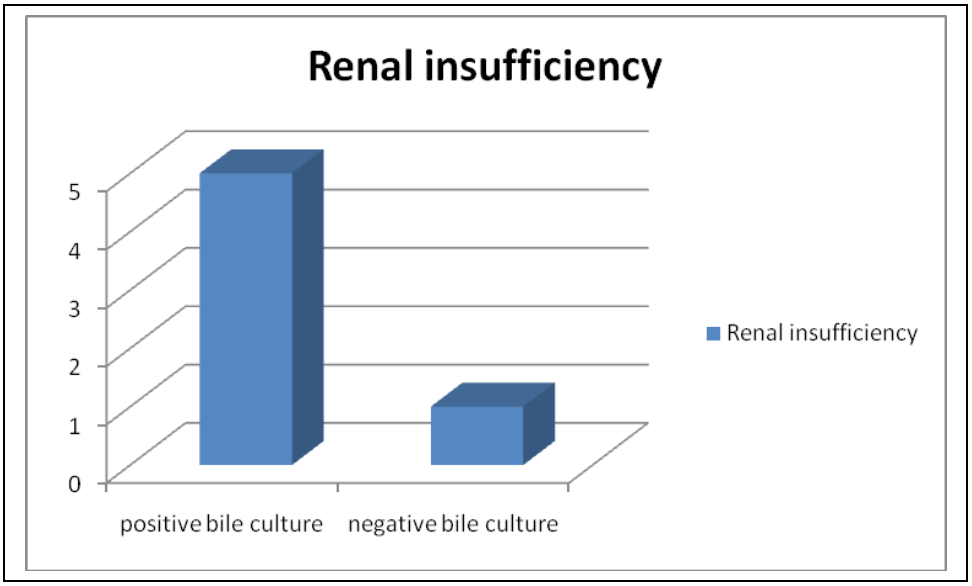
Major Complications

		0.95C.I Low	0.95 high
Odds ratio	3.36	0.99	11.36
Risk ratio	1.83	1.03	3.25

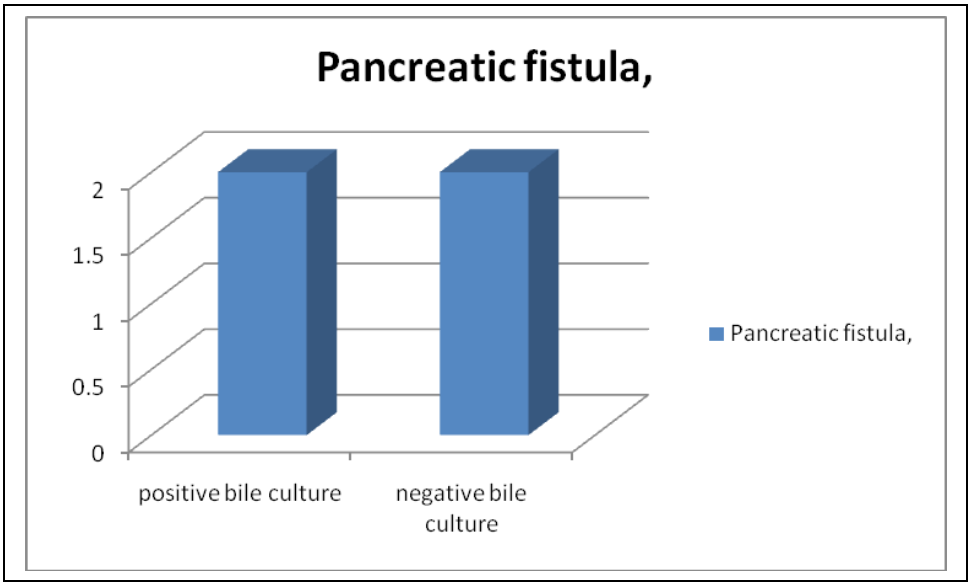
Patients in positive bile culture group had statistically increased indicence of renal insufficiency.(p=0.05). The odds ratio was 7.5 .The 0.95 Confidence interval was from 0.80 to 69. 63

Renal Insufficiency

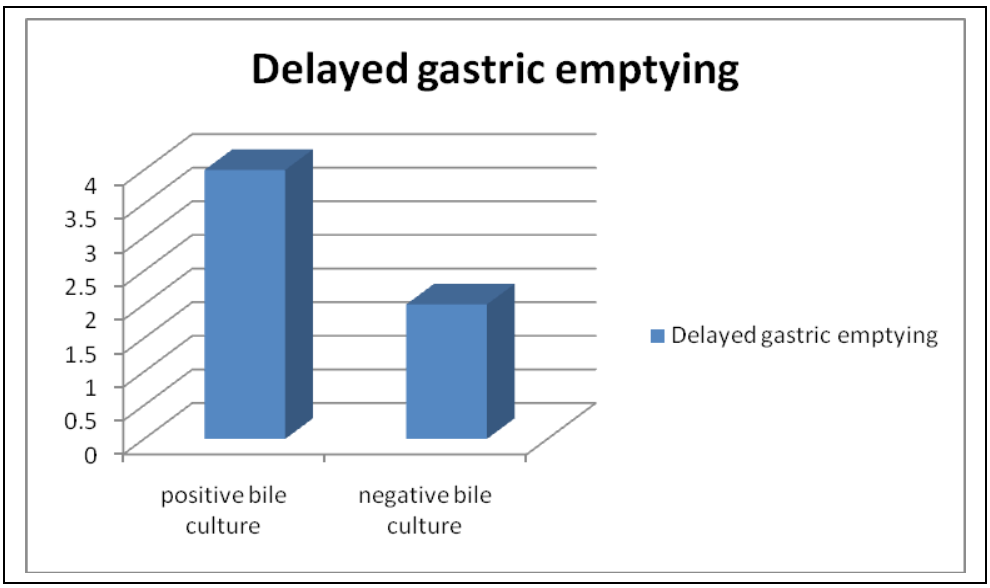
		0.95C.I Low	0.95C.I High
Odds ratio	7.5	0.80	69.63
Risk ratio	2.0	1.25	3.45



Association between positive bile culture & other complications like Pancreatic fistula (p=1), Delayed gastric emptying (p=0.3) , post pancreaticoduodenectomy haemorrhage (p=0.45) , pulmonary complications(p=1) were not significant.



It is worth to note that rate of these complication is low .

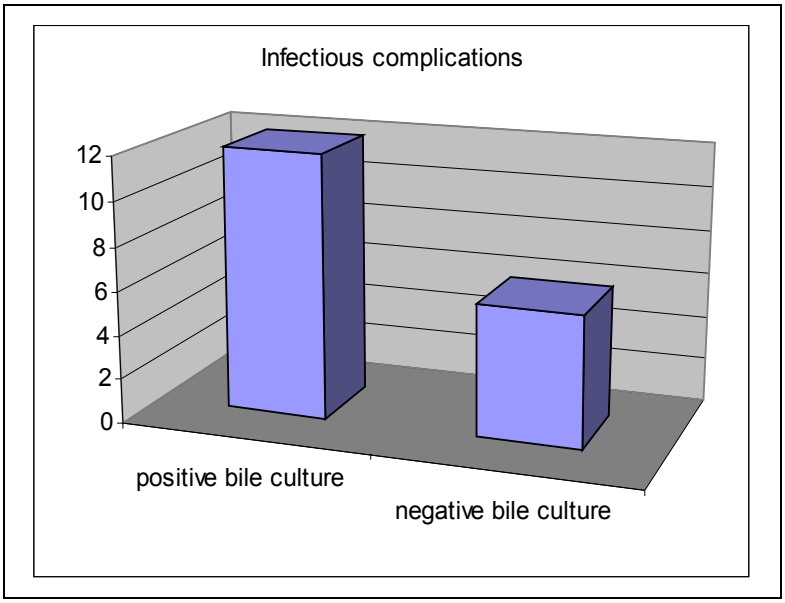


INFECTIOUS COMPLICATIONS

Table 4 . Postoperative Infectious Complications

Complications	Overall (n = 51) n	Positive bile culture (n = 23) N	Negative bile culture (n = 28) N	P Value
Infectious complications	18	12	6	0.022
Abscess*	4	4	0	0.035
Wound infection	18	12	6	0.022
Pneumonia	2	1	1	1 NS
Septicemia	7	6	1	0.03
Antibiotic therapy > 7 d	11	8	3	0.047

There is stastically significant incidence of Infectious complications in the positive bile culture group (p=0.022)



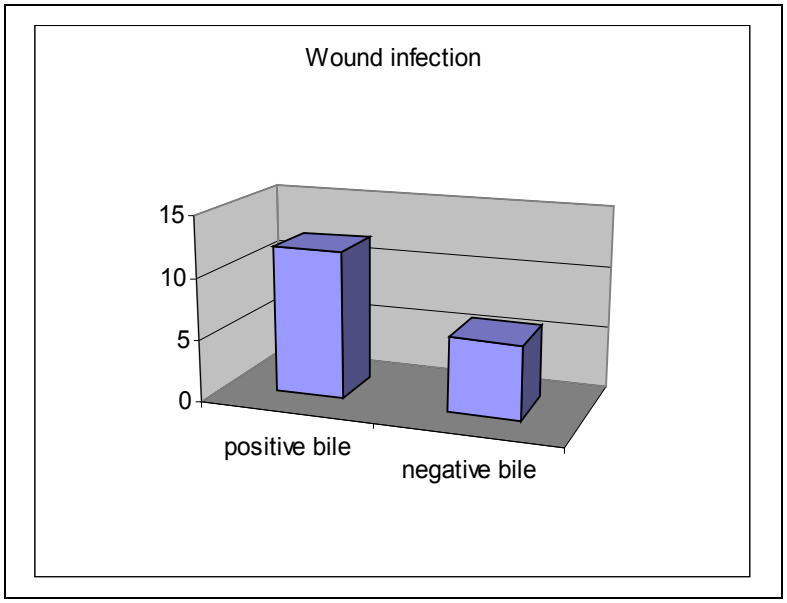
Infectious complications

		0.95C.I Low	0.95C.I High
Odds ratio	4	1.18	13.52
Risk ratio	2	1.11	3.58

There is statistically significant increase in wound infection (p = 0.022) ,Intra abdominal abscess (p=0.035), Septicemia (p=0.02), renal insufficiency (p=0.5685).

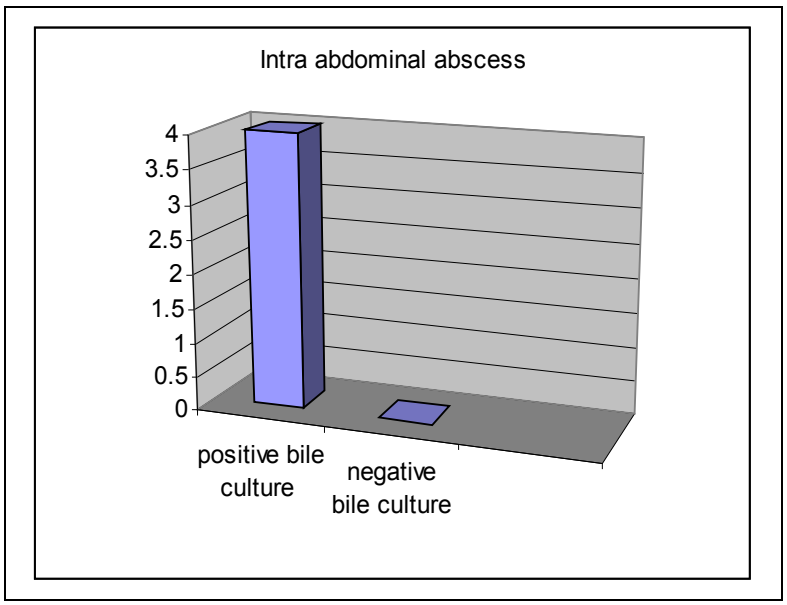
Wound Infection

		0.95C.I low	0.95C.I High
Odds ratio	4	1.18	13.52
Risk ratio	2	1.11	3.58



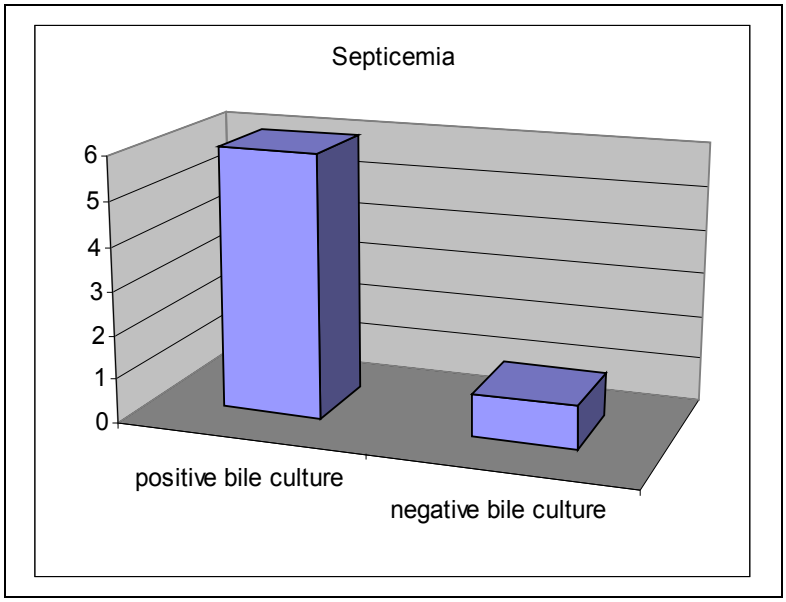
Intra Abdominal Abscess

		0.95C.I Low	0.95C.I High
Odds ratio	Infinity	NaN	Infinity
Risk ratio	2.47	1.74	3.5



Septicemia

		0.95C.I Low	0.95C.I High
Odds ratio	**9.52**	**1.05**	**86.20**
Risk ratio	**2.21**	**1.37**	**3.58**


Septicemia
6
5
4
3
2
1
0
positive bile culture
negative bile culture

BACTERIOLOGIC RESULTS

The organisms isolated were Escherichia coli, klebsiella sp, enterobacteriaceae, psuedomonos, & gram positive cocci. 34% of the cultures were poly microbial.E.coli was present in majority of isolates.

Table 5 . Microorganisms Isolated from Bile

Organisms	n	%
Gram-negative bacilli	34	94%
Escherichia coli	19	52%
Klebsiella sp	9	25%
Other *Enterobacteriaceae* *	1	3%
Psuedomonos	3	8%
Gram-positive cocci	2	5%
Enterococcus sp ‡	-	
Streptococcus sp	-	
Staphylococcus sp	2	5%
Yeast (candida sp)	-	
Citrobacter		

Most organisms were sensitive to piperacillin – tazo bactum , Amikacin & Gentamicin .

Resistance to quinolones(44%) , cephalosporins(53 – 95%) were high

Table 6 . Susceptibility to Antibiotics of Isolates from Intraoperative Bile

Antibiotic	Susceptible isolates	
	N	%
Piperacillin-tazobactam	30	83
Amikacin	30	83
Gentamicin	28	78
Ciprofloxacin	20	56
Cefotaxime	17	47
Amoxicillin-clavulanic acid	14	38
Cefazolin	1	5

	ERCP	No ERCP	P
Major complications	8/10	9/41	0.0011

Intra abdominal abscess	4/10	0/41	0.0008
Septicemia	6/10	1/41	0.00007
Renal failure	5/10	1/41	0.00058
Hospital stay	18.4	15.05	0.0002
Prolonged antibiotic Therapy > 7 days	8/10	3/41	0.00001

On analysis of the patients who had underwent ERCP vs others, for Major complications, intra abdominal abscess, septicemia, Renal failure , hospital & prolonged hospital stay, the ERCP group has statistically significant association with this variables. Patients undergone ERCP & stenting has more chance of developing , these complications, prolonged antibiotic therapy and hospital stay.

Major Complications

Odds ratio	**14**	**2.55**	**79.18**
Risk ratio	**8**	**1.90**	**33.63**

Intra abdominal abscess

Odds ratio	**Infinity**	**NaN**	**Infinity**
Risk ratio	**7.83**	**3.71**	**16.53**

Septicemia

Odds ratio	**60**	**5.70**	**631.25**
Risk ratrio	**9.42**	**3.53**	**25.17**

Renal Insufficiency

Odds ratio	**40**	**3.85**	**415.13**
Risk ratio	**7.5**	**3.04**	**18.45**

Prolonged antibiotic therapy

Odds ratio	**50.66**	**7.24**	**354.30**
Risk ratio	**14.54**	**3.59**	**58.89**

Hospital Stay

0.95 confidential interval difference from - 10.44 to 3. 58

DISCUSSION

Postoperative mortality of PD for periampullary tumor was close to 10% in the 1980s, justifying several clinical studies to improve postoperative course. It was suggested that preoperative jaundice as a strong determinant factor of postoperative complications and should be treated preoperatively.But neither randomized controlled trials nor retrospective comparative studies gave clear evidence that preoperative biliary drainage improves postoperative course after Pancreatocoduodenectomy.

Additionally, in 1999, Povoski and associates reported a higher rate of infectious complications in patients with preoperative biliary drainage, which has not been confirmed in two other large retrospective studies. Povoski and coworkers explained their results by the negative effect of bile contamination, which has also been reported as a major risk factor of postoperative sepsis after cholecystectomy and hepatectomy

Pancreaticoduodenectomy is nowadays done with a mortality of < 5% in major centers.But the morbidity of Pancreaticoduodenectomy has remained as high as 45% - 75% . Septic complications are responsible for one third of complications of pancreaticoduodenectomy . Pre operative biliary infection has been associated with increased post operative wound complications in many studies. This study demonstrates the association of positive bile culture to other septic complications like intra abdominal abscess, Septicemia , & Renal insufficiency .There is not only increase in

septic complications but in stented patients severe life threatening complications like septicemic shock & associated renal failure in this group of patients Role of pre operative biliary drainage in immediate post operative outcome is controversial . Meta analysis by Saleh et al concluded that no evidence was found of either a positive or adverse effect of preoperative endoscopic biliary stent placement on the outcome of surgery in patients with pancreatic cancer. Meta-analysis of level 1 studies showed no difference in the overall death rate between patients who had PBD and those who had surgery without PBD. The overall complication rate, however, was significantly adversely affected by PBD compared with surgery without PBD. In the

context of post pancreaticoduodenectomy complications the two Meta analysis has given controversial results. In our current study there is no significant increase in mortality in patients with positive bile culture. However, there is a statistically significant increase in the Major complication rate following positive bile culture & following preoperative biliary drainage in univariate analysis. But in Multivariate

analysis the major complications like intra abdominal abscess, septicemia & renal insufficiency was significantly increased in patients with positive bile culture . In multivariate analysis other major complications like Pancreatic fistula , delayed gastric emptying , post pancreatidoduodenectomy haemorrhage is not increased significantly . It is important to note that the rate of pancreatic fistula , delayed gastric emptying & post

pancreatidoduodenectomy haemorrhage is itself very less in our series , which may be one of the reasons for the absence of statistically significant association with positive bile culture .

As demonstrated by Povoski et al & Belghiti et al in their study , there is significant association with Endoscopic stenting & positive bile culture in our study.80 percent of patients who underwent endoscopic stenting developed positive bile culture only in 20% the bile showed no culture

There is no association of biliary infection with preoperative Biochemical parameters, pathological types or demographic characters as shown Belghiti et al. Co morbid conditions did not increase the likelihood of infected bile in our study.There was no difference between groups in intraoperative parameters –operating time , blood loss in our study.

CONCLUSION

In conclusion, Infected bile increases the post operative complications and associated with life threatening septicemia & renal insufficiency. Endoscopic stenting increases the risk of bactibilia, and post operative complications. Endoscopic stenting should be done only to strictly indicated patients. In patients with bactibilia intra operative spillage should be kept minimum & should be carefully followed post operatively to identify this complications and treated promptly .In view of increased septic complications , life threatening septicemia and renal failure in this patients with positive bile culture especially with preoperative biliary stenting , we advocate routine intra operative bile culture in all cases, specific antibiotic prophylaxis in patients with significant bactibilia in Gram stain smear & positive bile culture depending on the sensitivity patterns in the treating institution.

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